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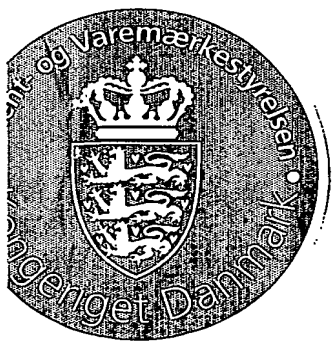

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PATENT- OG VAREMÆRKESTYRELSEN

NOVEL COMPLEXES OF BETA-2 ADRENOCEPTOR AGONISTS AND AMINOSUGARS

FIELD OF THE INVENTION

The present invention relates to a chemical complex comprising a beta-2 adrenoceptor agonist and an aminosugar. The combination of a beta-2 adrenoceptor agonist and an aminosugar in the preparation of a pharmaceutical product for the immunomodulation of a mammal, such as the suppression of hypersensitivity and inflammatory reactions, is disclosed herein.

BACKGROUND OF THE INVENTION

Hypersensitivity is defined as a state of altered reactivity in which the body reacts with an exaggerated immune response to a substance (antigen). Hypersensitivity may be caused by exogenous or endogenous antigens. Hypersensitivity reactions underlie a large number of diseases. Among these, allergic and autoimmune conditions are of great importance. A classification of hypersensitivity diseases is given in the textbook Clinical Medicine (Kumar, P. and Clark, M.: "Clinical Medicine", 3rd edition, p. 147-150, 1994, Bailliere Tindall, London).

Type I hypersensitivity reactions (IgE mediated allergic reactions) are caused by allergens (specific exogenous antigens), e.g. pollen, house dust, animal dandruff, moulds, etc. Allergic diseases in which type I reactions play a significant role include asthma, eczema (atopic dermatitis), urticaria, allergic rhinitis and anaphylaxis.

Type II hypersensitivity reactions are caused by cell surface or tissue bound antibodies (IgG and IgM) and play a significant role in the pathogenesis of myasthenia gravis, Goodpasture's syndrome and Addisonian pernicious anaemia.

Type III hypersensitivity reactions (immune complex) are caused by autoantigens or exogenous antigens, such as certain bacteria, fungi and parasites. Diseases in which type III hypersensitivity reactions play a significant role include lupus erythematosus, rheumatoid arthritis and glomerulonephritis.

Type IV hypersensitivity reactions (delayed) are caused by cell or tissue bound antigens. This type of hypersensitivity plays a significant role in a number of conditions, e.g. graft-versus-host disease, leprosy, contact dermatitis and reactions due to insect bites.

Type I to type IV hypersensitivity reactions are all classically allergic reactions, which may lead to histamine release. However, hypersensitivity reactions are also those, where

histamine release is triggered through the directly action of "triggering substances" with the cellular membrane. Examples of "triggering substances" are, but not limited to, toxins, food constituents and certain drugs.

A number of drug classes are available for the treatment of hypersensitivity reactions. Among these, the corticosteroids are some of the most widely used drugs. Corticosteroids primarily exert their pharmacological action by non-selectively inhibiting the function and proliferation of different classes of immune cells resulting in suppression of hypersensitivity reactions. Unfortunately, the corticosteroids are associated with a number of serious side effects, e.g. immunosuppression, osteoporosis and skin atrophy.

Cancer is caused by an uncontrolled proliferation of cells that express varying degrees of fidelity to their precursors. These cancer cells form a malignant tumour that enlarges and may spread to adjacent tissues or through blood and lymph systems to other parts of the body. There are numerous forms of cancer of varying severity. For most types of cancer there is no effective treatment today.

Aminosugars are the building blocks for the *in vivo* generation of glycosaminoglycans, formerly known as mucopolysaccharides. Glycosaminoglycans are constituents in various tissues in numerous mammals, both vertebrates and invertebrates and important examples of glycosaminoglycans are the chondroitin sulfates and the keratan sulfates in connective tissue, the dermatan sulfates in skin tissue, and hyaluronic acid in skin tissue and synovial joint fluid.

Administration of aminosugars or glycosaminoglycans in pharmacological doses to individuals suffering from osteoarthritis has resulted in some relief of symptoms and nowadays the use of aminosugars as chondroprotective agents is widely recognised.

The sympathetic nervous system is important in regulating organs such as the heart and the peripheral vasculature. The primary transmitter released from sympathetic nerve endings is nor adrenaline, but in some forms of stress adrenaline is also released from the adrenal medulla. The chatecholamines are inactivated primarily by reuptake.

Sympathomimetics are drugs that partially or completely mimic the actions of noradrenaline or adrenaline. They act either directly on alpha- and/or beta-adrenoceptors or indirectly on the presynaptic terminals usually by causing the release of noradrenaline. The effects of adrenoceptor stimulation are various. Beta-2 adrenoceptor agonists cause bronchodilation and are used in the treatment of asthma. They are also used to relax uterine muscle in an attempt to prevent preterm labour. Beta-2 adrenoceptor activation results in stimulation of adenylate cyclase, increasing the conversion of ATP to cyclic AMP. Beta-1 receptor agonists are used to stimulate the force of heart contraction in severe low-output heart failure. Alpha-1 agonists are used as mydriatics and in decongestant preparations. Alpha-2 agonists are used as centrally acting hypotensive drugs.

SUMMARY OF THE INVENTION

It has been found by the present investigator that a chemical complex or a pharmaceutical composition comprising a beta-2 adrenoceptor agonist and an aminosugar and optionally a pharmaceutically acceptable carrier significantly suppresses hypersensitivity reactions and are of use generally in the immunomodulation of a mammal, such as a human.

Contrarily to existing therapeutic agents, such as corticosteroids or non-steroidal anti-inflammatory drugs, the chemical complexes and pharmaceutical compositions according to the present invention have the advantage of not being likely to be associated with any serious side effects, as all of their components are non-toxic and well tolerated by the organism in the pharmacologically relevant doses.

Accordingly, the present invention provides a chemical complex or a pharmaceutical composition comprising:
i) a beta-2 adrenoceptor agonist; and
ii) an aminosugar; and optionally
iii) a pharmaceutically acceptable carrier or carrier.

The chemical complexes and pharmaceutical compositions according to the invention may be employed for therapeutic applications such as i) immunomodulation, ii) the treatment or prevention of hypersensitivity diseases; iii) the treatment or prevention of IgE mediated allergic reactions and conditions; iv) the treatment or prevention of autoimmune disorders; v) the alleviation of pain; vi) the treatment or prevention of cancer.

An important aspect of the invention relates to the use of a combination of a beta-2 adrenoceptor agonist and an aminosugar for the preparation of a product for the immunomodulation of a mammal, such as a human, as well as to a method for immunomodulation in a mammal, such as a human, comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, pharmaceutically acceptable salts thereof, or a complex comprising said combination or said salts to said mammal.

Still further aspects of the invention relate to a method for the suppression of hypersensitivity and/or inflammatory reaction in a mammal; a method for the treatment of hypersensitivity skin diseases, of atopic eczema, contact dermatitis, seborrhoeic eczema and/or psoriasis; of IgE mediated allergic reaction; of asthma, allergic rhinitis, and/or anaphylaxis; of autoimmune disease and/or chronic inflammatory disease; of diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout or osteoarthritis;of cancer; and to a method for the alleviation of pain in a mammal; each method comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, pharmaceutically acceptable salts thereof, or a complex or composition comprising said combination or said salts to said mammal.

Moreover, a still further aspect of the invention relates to a process for the preparation of a complex comprising i) a beta-2 adrenoceptor agonist; and ii) an aminosugar, comprising the steps of:
i) dissolving said beta-2 adrenoceptor and said aminosugar in a volatile solvent or a mixture of volatile solvents; and
ii) removing said suitable solvent so as to obtain a moisture content of at the most 5% w/w.

DETAILED DESCRIPTION OF THE INVENTION

The chemical complex comprising a beta-2 adrenoceptor agonist and an aminosugar significantly suppresses hypersensitivity reactions. Such chemical complexes are novel and provide a surprisingly good anti-hypersensitivity and anti-inflammatory effect with a surprisingly good safety profile. Thus the chemical complexes or compositions of the invention are virtually non-toxic and yet very therapeutically effective. The present inventor proposes the hypothesis that the very advantageous therapeutic index of the combination of an beta-2 adrenoceptor agonist and an aminosugar in comparison to the singular chemical anti-hypersensitivity drugs is due to synergistic effects between the components of the compositions, resulting in a lower toxic load on the body of any single chemical compound and yet providing a surprisingly good therapeutic effect.

The invention is based, at least in part, on the synergistic activity of the aminosugar with the beta-2 adrenoceptor agonist in comparison to either component. This surprising synergism allows for the combining of any compound which exhibits beta-2 adrenoceptor agonism with an amino sugar to achieve the desired effect at much lower doses of said H1-receptor antagonist compound than ever anticipated. Moreover, the synergism allows for the use of beta-2 adrenoceptor agonists previously not used for the desired effect due to the high doses required to achieve said effect. Still further, this synergism allows for the use of compounds, which are not used as beta-2 adrenoceptor agonists due to the toxicity associated with therapeutically effective doses.

The chemical complexes or compositions of the invention provide pharmacological effects upon administration to the living organism such as immunomodulation, suppression of hypersensitivity reactions, suppression of IgE mediated allergic reactions, suppression of autoimmune reactions, reduction of pain, and suppression of cancer.

Accordingly, the present invention relates to a chemical complex comprising:
i) a beta-2 adrenoceptor agonist; and
ii) an aminosugar.

The term chemical complex is intended to mean any combination of the component molecules. It is not intended necessarily to imply an ionic or otherwise association between the components.

In the present invention, the term "aminosugar" is intended to mean one or more amino derivatives of a monosaccharide (aldoses and ketoses) and its corresponding sugar alcohols (alditols) such as trioses, tetroses, pentoses, hexoses, heptoses and octoses. The aldose, ketose, or alditol has one or more hydroxy groups replaced by any amino group at any position, including the anomeric position. An aminosugar is thus a deoxyamino derivative of an aldose, ketose, or alditol. The term is also intended to mean polyamino sugars, wherein more than one hydroxy group has been replaced by an amino group (e.g. dideoxydiamino-, trideoxytriamino-derivatives).

The term "aminosugar" is also intended to mean amino derivatives of di-, oligo- and poly-saccharides comprising at least one of said monosaccharides. Consequently, in the case of di-, oligo- and poly-saccharides, the amino group may be position of glycosidation. Suitably, in di-, oligo- and poly-saccharides, the amino group may not be the position of glycosidation.

An amino group of an aminosugar may be alkylated, arylated or acylated or, alternatively, present as its free amine form (NH_2). Similarly, the hydoxyl groups may be optionally protected or derivatised such as alkylated, arylated or acylated or, alternatively, present in its free hydroxyl form.

The amine of the amino sugar may exist as its quaternary ammonium salt, using organic or mineral acids, as is known to the person skilled in the art. Furthermore, other fucntional groups on the aminosugar may be in the form of a salt. Similarly, prodrug derivatives of the aminosugar are anticipated by the present inventor. The prodrug form may be the result of the derivatisation of the amino group or another functional group present on the aminosugar, as is known to the person skilled in the art.

Furthermore, an aminosugar may have one or more hydroxy groups replaced by any amino group at any position and a further one or more hydroxy groups replaced by a hydrogen (a deoxy sugar), a thiol (a thiosugar), a halogen (a deoxyhalo sugar), an anhydrosugar (a sugar preparable via an intramolecular displacement with a hydroxyl to form an oxirane or oxetane), a carbonyl group.

Furthermore, the term aminosugar is denoted to mean aminosugars as described *supra* but optionally substituted.

The term "optionally substituted" is intended to mean the substitution of one or more hydrogen atoms, which is substituted with another atom, chemical group or entity, termed substituents. Illustrative examples of substituents include carboxyl, formyl, amino, hydroxyl, halogen, nitro, sulphono, sulphanyl, C_{1-6}-alkyl, aryl, aryloxy, aryloxycarbonyl, arylcarbonyl, heteroaryl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyloxy, dihalogen-C_{1-6}-alkyl, trihalogen-C_{1-6}-alkyl, C_{1-6}-alkoxyl, oxo, C_{1-6}-carboxyl, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl,

where aryl and heteroaryl representing substituents may be substituted 1-5 times with C_{1-6}-alkyl, C_{1-6}-alkoxy, nitro, cyano, hydroxy, amino or halogen. In general, the above substituents may be susceptible to further optional substitution.

The term "halogen" includes fluorine, chlorine, bromine and iodine.

In a particularly suitable embodiment of the invention, the aminosugar is sulphated or phosphorylated at the anomeric, 2-, 3-, 4-, or 6- position, typically at the 2-, 3-, or 4-position. In another suitable embodiment of the invention the aminosugar is N-acetylated.

Furthermore, a combination of suitable embodiments include the aminosugar sulphated or phosphorylated as well as in its salt form having Na^+; K^+; Mg^{++}; Ca^{++}; or NH_4^+ as counter ions.

Particularly suitable aminosugars according to the invention are selected from the group consisting of glucosamine, galactosamine and mannosamine, derivatives and salts thereof, typically glucosamine sulfate, glucosamine hydrochloride, N-acetylglucosamine, galactosamine sulfate, galactosamine hydrochloride, N-acetylgalactosamine, mannosamine sulfate, mannosamine hydrochloride, N-acetylmannosamine, as well as other aminosugars known to the person skilled in the art.

In a suitable embodiment, di-, oligo-, and poly-saccharides comprising of at least one aminosugar is comprised in the complex. In the embodiment wherein the aminosugar is an oligo- or polysaccharide, said oligo- or polysaccharide preferably consists of more than one aminosugar monosaccharide.

In a suitable embodiment of the invention, the chemical complex and the composition comprises more than one aminosugar.

The chemical complex of the present invention relates to a complex obtainable from the combining of a beta-2 adrenoceptor agonist and an aminosugar.

As stated, the complex comprises, in part, the Beta-2 adrenoceptor agonist which may be any chemical with the ability to stimulate the beta-2 adrenoceptor or parts thereof.

The Beta-2 adrenoceptor agonist, for illustrative purposes, may be selected from the group consisting of bambuterol, bitolterol, carbuterol, clenbuterol, clorprenaline, dioxethedrine, dopexamine, ephedrine, epinephrine, etafedrine, ethylnorepinephrine, fenoterol, formoterol, hexoprenaline, isoetharine, isoproterenol, mabuterol, metaproterenol, methoxyphenamine, pirbuterol, procaterol, protokylol, reproterol, rimiterol, ritodrine, salbutamol (albuterol), salmeterol, soterenol, terbutaline, tretoquinol, tulobuterol, derivatives and salts thereof.

The molar ratio between the Beta-2 adrenoceptor agonist and the aminosugar may be about 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, such as about 1:500 to

500:1, such as 1:100 to 100:1, about 1:50 to 50:1, or about 1:40 to 40:1, also about 1:30 to 30:1, such as about 1:25 to 25:1, about 1:20 to 20:1, about 1:18 to 18:1, about 1:16 to 16:1, about 1:14 to 14:1, or about 1:12 to 1:12, also about 1:10 to 10:1, such as about 1:9 to 9:1, about 1:8 to 8:1, about 1:7 to 7:1, about 1:6 to 6:1, also from 1:5 to 5:1, such as from 1:4 to 4:1, e.g. from 1:3 to 3:1, such as from 1:2 to 2:1.

Alternatively defined, the ratio between the Beta-2 adrenoceptor agonist and the aminosugar may be expressed as a mass ratio. The mass ratio between the Beta-2 adrenoceptor agonist and the aminosugar may be about 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, such as about 1:500 to 500:1, such as 1:100 to 100:1, about 1:50 to 50:1, or about 1:40 to 40:1, also about 1:30 to 30:1, such as about 1:25 to 25:1, about 1:20 to 20:1, about 1:18 to 18:1, about 1:16 to 16:1, about 1:14 to 14:1, or about 1:12 to 1:12, also about 1:10 to 10:1, such as about 1:9 to 9:1, about 1:8 to 8:1, about 1:7 to 7:1, about 1:6 to 6:1, also from 1:5 to 5:1, such as from 1:4 to 4:1, e.g. from 1:3 to 3:1, such as from 1:2 to 2:1.

For the administration to a mammal, the chemical complex may be formulated into a composition comprising the chemical complex and optionally, one or more acceptable excipients.

According to the invention, the above-mentioned chemical complexes or compositions may be combined with any other therapeutically active agents in order to strengthen, improve, potentiate, or prolong the therapeutic actions of said complexes and said compositions. Thus according to the invention, the composition may further comprise one or more therapeutically active agents.

The compositions according to the present invention may be formulated for oral, topical, transdermal, or parenteral administration, preferably oral or topical administration. The compositions according to the present invention may be formulated as a pharmaceutical composition for oral, topical, transdermal, or parenteral administration, preferably oral or topical administration.

In a suitable embodiment of the invention, the compositions are used for oral administration. In another suitable embodiment of the invention the compositions are used for topical administration.

The Beta-2 adrenoceptor agonist and the aminosugar may together be comprised in a single formulation or may each individually be comprised in separate formulations. The separate formulations may be administered in a simultaneous or non-simultaneous manner. As stated, the Beta-2 adrenoceptor agonist and the aminosugar are together comprised in a single formulation.

The active ingredients of the chemical complex or pharmaceutical composition of the present invention need not be administered as one pharmaceutical entity, but may of course be administered as individual compounds or pharmaceutical compositions.

In addition to the formulations described previously, the compositions of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions for oral, topical, transdermal, or parenteral administration may be in form of, e.g., solid, semi-solid or fluid compositions and formulated according to conventional pharmaceutical practice, see, e.g., "Remington: The science and practice of pharmacy" 20th ed. Mack Publishing, Easton PA, 2000 ISBN 0-912734-04-3 and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988 ISBN 0-8247-2800-9.

The choice of pharmaceutically acceptable excipients in a composition for use according to the invention and the optimum concentration thereof is determined on the basis of the selection of the Beta-2 adrenoceptor agonist, selection of the aminosugar, the kind of dosage form chosen and the mode of administration. However, a person skilled in the art of pharmaceutical formulation may find guidance in e.g., "Remington: The science and practice of pharmacy" 20th ed. Mack Publishing, Easton PA, 2000 ISBN 0-912734-04-3. A pharmaceutically acceptable excipient is a substance, which is substantially harmless to the individual to which the composition will be administered. Such an excipient suitably fulfils the requirements given by the national drug agencies. Official pharmacopeias such as the British Pharmacopeia, the United States of America Pharmacopeia and the European Pharmacopeia set standards for well-known pharmaceutically acceptable excipients.

For topical, trans-mucosal and trans-dermal compositions, such as administration to the mucosa or the skin, the compositions for use according to the invention may contain conventional non-toxic pharmaceutically acceptable carriers and excipients including microspheres and liposomes.

The topical, trans-mucosal and trans-dermal compositions for use according to the invention include an array of solid, semi-solid and fluid compositions. Compositions of particular relevance are e.g. pastes, ointments, hydrophilic ointments, creams, gels, hydrogels, solutions, emulsions, suspensions, lotions, liniments, resoriblets, suppositories, enema, pessaries, moulded pessaries, vaginal capsules, vaginal tablets, shampoos, jellies, soaps, sticks, sprays, powders, films, foams, pads, sponges (e.g. collagen sponges), pads, dressings (such as, e.g., absorbent wound dressings), drenches, bandages, plasters and transdermal delivery systems.

The pharmaceutically acceptable excipients for topical, trans-mucosal and trans-dermal compositions may include solvents, buffering agents, preservatives, humectants, chelating agents, antioxidants, stabilizers, emulsifying agents, suspending agents, gel-forming agents, ointment bases, suppository bases, penetration enhancers, perfumes, skin

protective agents, diluents, disintegrating agents, binding agents, lubricants and wetting agents.

The oral compositions for use according to the invention include an array of solid, semi-solid and fluid compositions. Compositions of particular relevance are e.g. solutions, suspensions, emulsions, uncoated tablets, immediate-release tablets, modified-release tablets, gastro-resistant tablets, orodispersible tablets, efferverscent tablets, chewable tablets, soft capsules, hard capsules, modified-release capsules, gastro-resistant capsules, uncoated granules, effervescent granules, granules for the preparation of liquids for oral use, coated granules, gastro-resistant granules, modified-release granules, powders for oral adminstration and powders for the preparation of liquids for oral use.

The pharmaceutically acceptable excipients may include solvents, buffering agents, preservatives, humectants, chelating agents, antioxidants, stabilizers, emulsifying agents, suspending agents, gel-forming agents, diluents, disintegratig agents, binding agents, lubricants, coating agents and wetting agents.

Typical solvents may be selected from the group comprising water, alcohols, vegetable or marine oils (e.g. edible oils like almond oil, castor oil, cacao butter, coconut oil, corn oil, cottonseed oil, linseed oil, olive oil, palm oil, peanut oil, poppyseed oil, rapeseed oil, sesame oil, soybean oil, sunflower oil, and teaseed oil), mineral oils, fatty oils, liquid paraffin, polyethylene glycols, propylene glycols, glycerol, liquid polyalkylsiloxanes, and mixtures thereof.

Typical buffering agents may be selected from the group comprising of citric acid, acetic acid, tartaric acid, lactic acid, hydrogenphosphoric acid, diethylamine etc.

Typical preservatives may be selected from the group comprising parabens, such as methyl, ethyl, propyl p-hydroxybenzoate, butylparaben, isobutylparaben, isopropylparaben, potassium sorbate, sorbic acid, benzoic acid, methyl benzoate, phenoxyethanol, bronopol, bronidox, MDM hydantoin, iodopropynyl butylcarbamate, EDTA, benzalconium chloride, and benzylalcohol, or mixtures of preservatives.

Typical humectants may be selected from the group comprising glycerin, propylene glycol, sorbitol, lactic acid, urea, and mixtures thereof. Typical chelating agents are but not limited to sodium EDTA and citric acid. Typical antioxidants may be selected from the group comprising butylated hydroxy anisole (BHA), ascorbic acid and derivatives thereof, tocopherol and derivatives thereof, cysteine, and mixtures thereof. Suitable emulsifying agents may be selected from the group comprising naturally occurring gums, e.g. gum acacia or gum tragacanth; naturally occurring phosphatides, e.g. soybean lecithin; sorbitan monooleate derivatives; wool fats; wool alcohols; sorbitan esters; monoglycerides; fatty alcohols, fatty acid esters (e.g. triglycerides of fatty acids); and mixtures thereof.

Suitable suspending agents may be selected from the group comprising celluloses and cellulose derivatives such as, e.g., carboxymethyl cellulose, hydroxyethylcellulose,

hydroxypropylcellulose, hydroxypropylmethylcellulose, carrageenan, acacia gum, arabic gum, tragacanth, and mixtures thereof.

Suitable gel bases and viscosity-increasing components may be selected from the group comprising liquid paraffin, polyethylene, fatty oils, colloidal silica or aluminium, zinc soaps, glycerol, propylene glycol, tragacanth, carboxyvinyl polymers, magnesium-aluminium silicates, Carbopol®, hydrophilic polymers such as, e.g. starch or cellulose derivatives such as, e.g., carboxymethylcellulose, hydroxyethylcellulose and other cellulose derivatives, water-swellable hydrocolloids, carragenans, hyaluronates (e.g. hyaluronate gel optionally containing sodium chloride), and alginates including propylene glycol alginate.

Typical ointment bases may be selected from the group comprising beeswax, paraffin, cetanol, cetyl palmitate, vegetable oils, sorbitan esters of fatty acids (Span), polyethylene glycols, and condensation products between sorbitan esters of fatty acids and ethylene oxide, e.g. polyoxyethylene sorbitan monooleate (Tween).

Typical hydrophobic ointment bases may be selected from the group comprising paraffins, vegetable oils, animal fats, synthetic glycerides, waxes, lanolin, and liquid polyalkylsiloxanes. Typical hydrophilic ointment bases are but not limited to solid macrogols (polyethylene glycols).

Suitable powder components may be selected from the group comprising alginate, collagen, lactose, powder, which is able to form a gel when applied to a wound (absorbs liquid/wound exudate).

Suitable diluents and disintegrating agents may be selected from the group comprising lactose, saccharose, emdex, calcium phosphates, calcium carbonate, calcium sulphate, mannitol, starches and microcrystaline cellulose.

Suitable binding agents may be selected from the group comprising saccharose, sorbitol, gum acacia, sodium alginate, gelatine, starches, cellulose, sodium carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone and polyetyleneglycol.

Typical wetting agents may be selected from the group comprising sodium laurylsulphate and polysorbate 80.

Suitable lubricants may be selected from the group comprising talcum, magnesium stearate, calcium stearate, silicium oxide, precirol and polyethylenglycol.

Suitable coating agents may be selected from the group comprising hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpropylidone, ethylcellulose and polymethylacrylates.

Typical suppository bases may be selected from the group comprising oleum cacao, adeps solidus and polyethylenglycols.

The composition comprises a beta-2 adrenoceptor agonist and an aminosugar as defined for the chemical complexes. Correspondingly, the composition of the present invention may comprise the complex as defined *supra*. Thus the aminosugar may be selected from the group consisting of glucosamine, galactosamine, mannosamine, derivatives and salts thereof, e.g. wherein the aminosugar is N-acetylglucosamine, N-acetylgalactosamine or N-acetylmannosamine. A preferred composition comprises glucosamine sulfate, glucosamine hydrochloride and/or N-acetylglucosamine.

Moreover, the molar ratio or mass ratio between the Beta-2 adrenoceptor agonist and the aminosugar in the composition may be as defined for the complex, as discussed *supra*.

The chemical complex or composition of the invention may be used for the preparation of a medicament for the treatment of diseases and disorders associated with the stimulation of beta-2 adrenoceptors.

The chemical complexes or compositions of the invention provide pharmacological effects upon administration to the living organism such as immunomodulation, suppression of hypersensitivity reactions, suppression of inflammatory reactions, suppression of IgE mediated allergic reactions, suppression of autoimmune reactions, reduction of pain, and suppression of cancer. Correspondingly, a further aspect of the invention relates to a method for immunomodulation in a mammal, such as a human, comprising the administration to said mammal of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof,
or a chemical complex comprising a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof.

The anti-inflammatory activity was demonstrated in the arachidonic acid induced ear inflammation test in mice, which is a commonly employed method for screening and evaluation of antiinflammatory drugs.

One aspect of the invention relates to a method for the treatment or prevention of hypersensitivity disease or inflammation comprising the administration of the above mentioned chemical complexes or compositions of the invention to a mammal, preferentially a human. The therapeutic action may be relevant to diseases associated with hypersensitivity reactions or inflammation in general. The action of the complex of the invention may be relevant to the treatment of conditions and diseases associated with hypersensitivity reaction, such as infections (viral, bacterial, fungal, parasitic), cold and flu, contact dermatitis, insect bites, allergic vasculitis, post-operative reactions, transplantation rejection (graft-versus-host disease), and so forth.

A further aspect of the invention relates to the use of a complex of the invention for the treatment of autoimmune disorders and IgE mediated allergic conditions.

Correspondingly, the invention further relates to a method for the treatment or prevention of autoimmune disorders comprising the administration of the chemical complexes or compositions of the invention to a mammal, preferentially a human.

Thus, a further aspect of the invention relates to the treatment of autoimmune disorders such as Autoimmune hepatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Autoimmune hemolytic anemias, Grave's disease, Myasthenia gravis, Type 1 Diabetes Mellitus, Inflammatory myopathies, Multiple sclerosis, Hashimoto's thyreoiditis, Autoimmune adrenalitis, Crohn's Disease, Ulcerative Colitis, Glomerulonephritis, Progressive Systemic Sclerosis (Scleroderma), Sjögren's Disease, Lupus Erythematosus, Primary vasculitis, Rheumatoid Arthritis, Juvenile Arthritis, Mixed Connective Tissue Disease, Psoriasis, Pemfigus, Pemfigoid, and Dermatitis Herpetiformis.

A still further aspect of the invention relates to a method for the treatment or prevention of an IgE mediated allergic reaction or condition comprising administration of the chemical complexes or compositions of the invention to a mammal, preferably to a human. The applicant proposes the hypothesis that the therapeutic action is due to the suppressing effect on hypersensitivity reactions of the above mentioned compositions. The therapeutic action may be relevant to IgE mediated allergic reactions and conditions in general such as asthma, eczema (e.g. atopic dermatitis), urticaria, allergic rhinitis, anaphylaxis.

Moreover, the chemical complex or composition of the present invention may be used in a method for the treatment or prevention of any condition associated with pain. The applicant proposes the hypothesis that the therapeutic action is related to immunomodulation, possibly to a suppressing effect on hypersensitivity reactions.

Accordingly, a further aspect of the invention relates to a use of a combination of a beta-2 adrenoceptor agonist and an aminosugar for the preparation of a medicament for the immunomodulation of a mammal, such as a human. The immunomodulation typically results in the suppression of hypersensitivity and suppression of inflammatory reactions. The immodulation may be associated with diseases and disorders selected from the group consisting of hypersensitivity skin disease, atopic eczema, contact dermatitis, seborrhoeic eczema, psoriasis, IgE mediated allergic reactions, asthma, allergic rhinitis, anaphylaxis, autoimmune disease, chronic inflammatory disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout, osteoarthritis, pain and cancer.

Accordingly, the chemical complexes or compositions of the invention are suitable for the treatment or prevention of diseases caused by inflammation of various tissues, such as the inflammation of the prostate, in particular prostatitis.

Still further, the chemical complexes or compositions of the invention may be employed for the treatment or prevention of cancer of any type and at any stage. The present inventor puts forward the hypothesis that the anticancer effect is due to a combination of immunomodulating and tumour-suppressing effects of the complexes and compositions of the invention.

A still further aspect of the invention relates to a process for the preparation of a complex comprising i) a beta-2 adrenoceptor agonist; and ii) an aminosugar, comprising the steps of:

i) dissolving said beta-2 adrenoceptor and said aminosugar in a volatile solvent or a mixture of volatile solvents; and
ii) removing said suitable solvent so as to obtain a moisture content of at the most 5% w/w.

In principle, a plethora of solvents and mixture of solvents can be used in the preparation of complexes according to the invention. Suitable solvents or mixture of solvents are those being substantially removed upon evaporation at room temperature, at elevated temperature, under atmospheric or reduced pressure, or upon spray drying or freeze-drying. Furthermore, solvents and mixture of solvents should be suitable for dissolving or at least partially dissolving said beta-2 adrenoceptor and said aminosugar at room temperature or optionally upon heating. In a preferred embodiment of the invention, the beta-2 adrenoceptor and said aminosugar are fully dissolved in the suitable solvent or mixture of suitable solvents. Preferably, no traces of undissolved beta-2 adrenoceptor and said aminosugar is present in the solution.

Thus, according to the invention the volatile solvent is selected from the group consisting of water, water-miscible, volatile organic solvents and mixtures thereof. Suitable water-miscible organic solvents is selected from the group consisting of methanol, ethanol, propanol, iso-propanol, butanol, iso-butanol, tert-butanol, acetone , acetic acid, acetonitrile, ethers, chloroform and dichlormethane. Further suitable solvents relates to organic solvents capable of both dissolving hydrophobic and hydrophilic substances, such as those organic solvents selected from the group consisting of dimethylsulfoxide and dimethylformamids. Moreover, any other azeotrope solvents is preferred.

As stated, the process for preparation of a complex comprises removing of solvent so as to obtain a complex that are essentially dry and in solid form. That is to say so as to form a complex with low moisture content. The moisture being residues of water and/or residues of the water miscible organic solvents. Thus, in a interesting embodiment of the invention, the moisture content is at the most 3% w/w, preferably at the most about 2% w/w, more preferably at the most about 1% w/w, even more preferably at the most about 0.5 % w/w, most preferably at the most about 0.2 % w/w.

EXAMPLES

The following examples describe the preparation of chemical complexes of the present invention.

General method example 1-164:
The beta-2 adrenoceptor agonist and the aminosugar derivative are dissolved in as little solvent as possible. The solvent is removed by spray drying or freeze-drying. After the solvent is removed the complex is a white to yellowish powder.
The solvent is water:ethanol in any v/v % combination.

The complex is suitable for any type of product *e.g.* pharmaceutical products, dietary supplements and cosmetic formulations. Non-limiting examples of such products are tablets, capsules, ointments and lotions as described above.

Example 1 to 32: Molar ratio Beta-2 adrenoceptor agonist/ aminosugar derivative 1:10000 (mol/mol).

	Beta-2 adrenoceptor agonist 1mol	Aminosugar 10000 mol
Example 1.	Salbutamol	Glucosamine
Example 2.	Bambuterol	Glucosamine HCl
Example 3.	bitolterol	Glucosamine sulfate
Example 4.	Carbuterol	Glucosamine 2 sulfate, free acid
Example 5.	Clenbuterol	Glucosamine 2 sulfate, Na^+ salt
Example 6.	Clorprenaline	Glucosamine 2 sulfate, K^+ salt
Example 7.	Dioxethedrine	N-acetylglucosamine 3,4,6 sulfate, tri Na^+ salt
Example 8.	Dopexamine	Galactosamine 3,6 sulfate, K^+ salt
Example 9.	Ephedrine	N-acetylgalactosamine
Example 10.	Epinephrine	N-acetylgalactosamine sulfate
Example 11.	Etafedrine	N-acetylglucosamine
Example 12.	Ethylnorepinephrine	Glucosamine 6 sulfate, Na^+ salt
Example 13.	Fenoterol	Glucosamine 3 sulfate, Na^+ salt
Example 14.	Formoterol	Galactosamine 3,6 sulfate, K^+ salt
Example 15.	Hexoprenaline	N-acetylgalactosamine
Example 16.	Isoetharine	Glucosamine HCl
Example 17.	Isoproterenol	Mannosamine HCl
Example 18.	Mabuterol	N-acetylmannosamine
Example 19.	Metaproterenol	Glucosamine sulfate
Example 20.	Methoxyphenamine	N-acetylglucosamin
Example 21.	Pirbuterol	N-acetylgalactosamine
Example 22.	Procaterol	N-acetylgalactosamine sulfate
Example 23.	Protokylol	N-acetylglucosamine
Example 24.	Reproterol	Glucosamine 6 sulfate, Na^+ salt

Example 25.	Rimiterol	Glucosamine 3 sulfate, Na^+ salt
Example 26.	Ritodrine	Galactosamine 3,6 sulfate, K^+ salt
Example 27.	Salbutamol	N-acetylgalactosamine
Example 28.	Salmetrol	Glucosamine HCl
Example 29.	Soterenol	Mannosamine HCl
Example 30.	Terbutaline	N-acetylmannosamine
Example 31.	Tretoquinol	Glucosamine sulfate
Example 32.	tulobuterol	N-acetylglucosamin

Example 33 to 51: Molar ratio Beta-2 adrenoceptor agonist / aminosugar derivative 1:6332 (mol/mol).

	Beta-2 adrenoceptor agonist 1mol	Aminosugar 6332 mol
Example 33.	formoterol fumerate dihydrate	N-acetylglucosamin
Example 34.	bambuterol HCl	Glucosamine 3 sulfate, Na^+ salt
Example 35.	Bitoltrol mesylate	Galactosamine 3,6 sulfate, K^+ salt
Example 36.	Clenbuterol HCl	N-acetylgalactosamine
Example 37.	Chlorprenaline HCl, H_2O	Glucosamine HCl
Example 38.	Dopexamine 2HCl	Glucosamine sulfate
Example 39.	Isoetharine	Glucosamine HCl
Example 40.	Isoproterenol	Mannosamine HCl
Example 41.	Mabuterol HCl	N-acetylmannosamine
Example 42.	Metaproterenol	Glucosamine sulfate
Example 43.	Methoxyphenamine HCl	N-acetylglucosamin
Example 44.	Pirbuterol monoacetate	N-acetylgalactosamine
Example 45.	Procaterol	N-acetylgalactosamine sulfate
Example 46.	Protokylol	N-acetylglucosamine
Example 47.	Reproterol HCl	Glucosamine 6 sulfate, Na^+ salt
Example 48.	Rimiterol HBr	Glucosamine 3 sulfate, Na^+ salt
Example 49.	Ritodrine HCl	Galactosamine 3,6 sulfate, K^+ salt
Example 50.	Salbutamol sulfate	N-acetylgalactosamine
Example 51.	Salmetrol	Glucosamine HCl

Example 52 to 73: Molar ratio Beta-2 adrenoceptor agonist / aminosugar derivative 1:1500 (mol/mol).

	Beta-2 adrenoceptor agonist 1mol	Aminosugar 1500 mol
Example 52.	Soterenol	N-acetylgalactosamine
Example 53.	Terbutaline	Glucosamine HCl

Example 54.	Tretoquinol HCl	Glucosamin 6 sulfate, free acid
Example 55.	Tulobuterol	Glucosamine sulfate
Example 56.	Salbutamol sulfate	N-acetylglucosamin HCl
Example 57.	Formoterol fumerate dihydrate	Glucosamin 3 sulfate, K^+ salt
Example 58.	Dopexamine	Galactosamine 3,6 sulfate, K^+ salt
Example 59.	Ephedrine	N-acetylgalactosamine
Example 60.	Epinephrine	N-acetylgalactosamine sulfate
Example 61.	Etafedrine	N-acetylglucosamine
Example 62.	Ethylnorepinephrine	Glucosamine 6 sulfate, Na^+ salt
Example 63.	Fenoterol HBr	Glucosamine 3 sulfate, Na^+ salt
Example 64.	Formoterol	Galactosamine 3,6 sulfate, K^+ salt
Example 65.	Isoproterenol sulfate dihydrate	Mannosamine HCl
Example 66.	Mabuterol	N-acetylmannosamine
Example 67.	Metaproterenol HCl	Glucosamine sulfate
Example 68.	Methoxyphenamine	N-acetylglucosamin
Example 69.	Salbutamol	N-acetylgalactosamine
Example 70.	Salmetrol	Glucosamine HCl
Example 71.	Soterenol	Mannosamine HCl
Example 72.	Terbutaline sulfate	N-acetylmannosamine
Example 73.	Tretoquinol	Glucosamine sulfate

Example 74 to 91: Molar ratio Beta-2 adrenoceptor agonist/ aminosugar derivative 1:405 (mol/mol).

	Beta-2 adrenoceptor agonist 1mol	Aminosugar 405 mol
Example 74.	Salbutamol	N-acetylglucosamin
Example 75.	bitolterol	Galactosamine
Example 76.	Carbuterol	Glucosamine HCl
Example 77.	Clenbuterol HCl	Glucosamine sulfate
Example 78.	Clorprenaline	Galactosamine 3,6 sulfate, di Na^+ salt
Example 79.	Dioxethedrine	N-acetylglucosamin HCl
Example 80.	Ethylnorepinephrine HCl	Glucosamine 6 sulfate, Na^+ salt
Example 81.	Fenoterol	Glucosamine 3 sulfate, Na^+ salt
Example 82.	Formoterol	Galactosamine 3,6 sulfate, K^+ salt
Example 83.	Isoproterenol	Mannosamine HCl
Example 84.	Mabuterol HCl	N-acetylmannosamine
Example 85.	Metaproterenol HCl	Glucosamine sulfate
Example 86.	Methoxyphenamine	N-acetylglucosamin
Example 87.	Salbutamol sulfate	N-acetylgalactosamine

Example 88.	Salmetrol	Glucosamine HCl
Example 89.	Soterenol HCl	Mannosamine HCl
Example 90.	Terbutaline sulfate	N-acetylmannosamine
Example 91.	Tretoquinol	Glucosamine sulfate

Example 92 to 115: Molar ratio Beta-2 adrenoceptor agonist/ aminosugar derivative 1:130 (mol/mol).

	Beta-2 adrenoceptor agonist 1mol	Aminosugar 130 mol
Example 92.	Salbutamol	Glucosamine sulfate
Example 93.	Clenbuterol	Galactosamine
Example 94.	Clorprenaline	N-acetylgalactosamine 3,6 sulfate, K^+ salt
Example 95.	Dioxethedrine	Glucosamine sulfate
Example 96.	Dopexamine	N-acetylglucosamine HCl
Example 97.	Ephedrine	N-acetylglucosamine 3 sulfate, free acid
Example 98.	Epinephrine	Galactosamine 4 sulfate, K^+ salt
Example 99.	Etafedrine	N-acetylgalactosamine 3,6 sulfate, Na^+ salt
Example 100.	Ethylnorepinephrine	Glucosamine 6 sulfate, K^+ salt
Example 101.	Fenoterol	Glucosamine 2,3 sulfate, di Na^+ salt
Example 102.	Formoterol fumerate dihydrate	N-acetylglucosamine HCl
Example 103.	Hexoprenaline	Glucosamine sulfate
Example 104.	Salmetrol	Glucosamine HCl
Example 105.	Soterenol	Mannosamine HCl
Example 106.	Terbutaline	N-acetylmannosamine
Example 107.	Tretoquinol	Glucosamine sulfate
Example 108.	Hexoprenaline	N-acetylgalactosamine
Example 109.	Isoetharine	Glucosamine HCl
Example 110.	Isoproterenol	Mannosamine HCl
Example 111.	Mabuterol	N-acetylmannosamine
Example 112.	Metaproterenol	Glucosamine sulfate
Example 113.	Methoxyphenamine	N-acetylglucosamin
Example 114.	Pirbuterol	N-acetylgalactosamine
Example 115.	Procaterol	N-acetylgalactosamine sulfate

Example 116 to 124: Molar ratio Beta-2 adrenoceptor agonist/ aminosugar derivative 1:19 (mol/mol).

	Beta-2 adrenoceptor agonist 1mol	Aminosugar 19 mol
Example 116.	Salbutamol	Glucosamine sulfate
Example 117.	Salbutamol sulfate	Glucosamine 2 sulfate, K^+ salt
Example 118.	Bitolterol	Galactosamine
Example 119.	Carbuterol	Glucosamine

Example 120.	Clenbuterol	N-acetylgalactosamine 4 sulfate, K^+ salt
Example 121.	Clorprenaline	N-acetyl-glucosamine HCl
Example 122.	Tretoquinol	Galactosamine 2 sulfate, Na^+ salt
Example 123.	Hexoprenaline	Mannosamine HCl
Example 124.	Isoetharine	N-acetylmannosamine

Example 125 to 137: Molar ratio Beta-2 adrenoceptor agonist/ aminosugar derivative 1:1 (mol/mol).

	Beta-2 adrenoceptor agonist 1mol	Aminosugar 1 mol
Example 125.	Bambuterol HCl	Glucosamine HCl
Example 126.	Bitoltrol mesylate	N-acetyl-glucosamine
Example 127.	Salbutamol	Galactosamine sulfate
Example 128.	Formoterol fumerate dihydrate	Glucosamine 3,4,6 sulfate, free acid
Example 129.	Tretoquinol HCl	N-acetylgalactosamine HCl
Example 130.	Hexoprenaline sulfate	N-acetylgalactosamine
Example 131.	Isoetharine	Glucosamine HCl
Example 132.	Isoproterenol	Mannosamine HCl
Example 133.	Mabuterol	N-acetylmannosamine
Example 134.	Metaproterenol sulfate	Glucosamine sulfate
Example 135.	Methoxyphenamine	N-acetylglucosamin
Example 136.	Pirbuterol 2HCl	N-acetylgalactosamine
Example 137.	Procaterol	N-acetylgalactosamine sulfate

Example 138 to 143: Molar ratio Beta-2 adrenoceptor agonist/ aminosugar derivative 5:1 (mol/mol).

	Beta-2 adrenoceptor agonist 5mol	Aminosugar 1 mol
Example 138.	Salbutamol	Galactosamine 4 sulfate, K^+ salt
Example 139.	Formoterol fumerate dihydrate	N-acetylglucosamin
Example 140.	Fenoterol HBr	N-acetylgalactosamine
Example 141.	Mabuterol	Mannosamine HCl
Example 142.	Methoxyphenamine HCl	N-acetylglucosamine HCl
Example 143.	Reproterol	Glucosamine sulfate

Example 144 to 148: Molar ratio Beta-2 adrenoceptor agonist / aminosugar derivative 50:1 (mol/mol).

	Beta-2 adrenoceptor agonist	Aminosugar 1 mol

	50mol	
Example 144.	Dioxethedrine	Glucosamine sulfate
Example 145.	Dopexamine 2HCl	N-acetylglucosamine
Example 146.	Ephedrine HCl	Galactosamine HCl
Example 147.	Epinephrine	N-acetylmannosamine
Example 148.	Salbutamol sulfate	N-acetylglucosamin HCl

Example 149 to 153: Molar ratio Beta-2 adrenoceptor agonist / aminosugar derivative 500:1 (mol/mol).

	Beta-2 adrenoceptor agonist 500mol	Aminosugar 1 mol
Example 149.	Rimiterol	Glucosamine sulfate
Example 150.	Bitolterol mesylate	N-acetylglucosamine
Example 151.	Salbutamol	Galactosamine HCl
Example 152.	Salmetrol xinafoate	Mannosamine
Example 153.	Clenbuterol HCL	N-acetylglucosamin HCl

Example 154 to 159: Molar ratio Beta-2 adrenoceptor agonist / aminosugar derivative 1000:1 (mol/mol).

	Beta-2 adrenoceptor agonist 1000mol	Aminosugar 1 mol
Example 154.	Mabuterol HCl	Glucosamine sulfate
Example 155.	Clenbuterol	N-acetylglucosamine
Example 156.	Salbutamol sulfate	Galactosamine HCl
Example 157.	Tulobuterol HCl	N-acetylgalactosamine 3,6 sulfate, di Na^+ salt
Example 158.	Ritodrine HCl	N-acetylglucosamin HCl
Example 159.	Protokylol	Mannosamine HCl

Example 160 to 164: Molar ratio Beta-2 adrenoceptor agonist / aminosugar derivative 10000:1 (mol/mol).

	Beta-2 adrenoceptor agonist 10000mol	Aminosugar 1 mol
Example 160.	Pirbuterol 2HCl	Glucosamine sulfate
Example 161.	Methoxyphenamine	N-acetylglucosamine
Example 162.	salbutamol	Galactosamine HCl
Example 163.	Isoetharine	N-acetylgalactosamine 3,6 sulfate, di Na^+ salt
Example 164.	Fenoterol HCl	N-acetylglucosamin HCl

General method example 165-176:
A quantity of the Beta-2 adrenoceptor agonist and the aminosugar derivative are transferred to a hard gelatine capsule.

Example 165 to 170: Capsule 500 mg, molar ratio Beta-2 adrenoceptor agonist/ aminosugar derivative 1:1000 (mol/mol).

	Beta-2 adrenoceptor agonist 1mol	Aminosugar 1000 mol
Example 165.	Salbutamol 239.31g/mol 0.55mg	Glucosamin HCl 215.6g/mol 499.45mg
Example 166.	Salbutamol sulfate 576.7g/mol 1.3mg	N-acetylglucosamine 221.2g/mol 498.7mg
Example 167.	Formoterol fumerate dihydrate 840.91g/mol 0.7mg	Glucosamine sulfate 605.1g/mol 499.3mg
Example 168.	Formoterol 344.41g/mol 0.8mg	Galactosamine HCl 215.6g/mol 499.2mg
Example 169.	Fenoterol 303.36g/mol 0.7mg	Mannosamine HCl 215.6g/mol 499.3mg
Example 170.	Mabuterol 310.75g/mol 0.7mg	N-acetylmannosamine 221.2g/mol 499.3mg

Example 171 to 176: Capsule 750 mg, molar ratio Beta-2 adrenoceptor agonist/ aminosugar derivative 1:53(mol/mol).

	Beta-2 adrenoceptor agonist 1mol	Aminosugar 53 mol
Example 171.	Dopexamine 356.51g/mol 22.7mg	Glucosamin HCl 215.6g/mol 727.3mg
Example 172.	Salbutamol sulfate 576.7g/mol 35.16mg	N-acetylglucosamine 221.2g/mol 714.84mg
Example 173.	Formoterol fumerate dihydrate 840.91g/mol 19.16mg	Glucosamine sulfate 605.1g/mol 730.84mg
Example 174.	Salbutamol 239.31g/mol 15.0mg	N-acetylglucosamine 221.2g/mol 735.0mg
Example 175.	Ephedrine 165.24g/mol 10.4mg	N-acetylmannosamine 221.2g/mol 739.6mg
Example 176.	Formoterol 344.41g/mol 21.94mg	Glucosamin HCl 215.6g/mol 728.06mg

Example 177

Objective

The objective of this study is to assess the effect of three doses of two chemical complexes of the invention systemically administered in the arachidonic acid induced ear inflammation test in the mouse, a commonly employed method for screening and evaluation of antiinflammatory drugs. Dexamethasone was employed as reference compound.

Test articles and vehicle

The test articles are the complexes of the invention prepared according to example 33 and example 92 (Compound 33 and Compound 92 in the following). Compound 33, Compound 92 and dexamethasone are obtained from Astion A/S, Denmark.

Animals

The study was performed in female BALB/ca mice from M & B A/S, DK-8680 Ry. At start of the acclimatisation period the mice were in the weight range of 20 g (+/- 5g).

Housing

The study took place in an animal room provided with filtered air. The temperature in the room was set at 21 - 23°C and the relative humidity to ≥30%. The room was illuminated to give a cycle of 12 hours light and 12 hours darkness. Light was on from 06.00 till 18.00 h.

The animals were housed in Macrolon type III cages (40x25x14 cm), 10 in each cage. The cages were cleaned and the bedding changed at least once a week.

Bedding

The bedding was sawdust (Tapvei 4HV) from Tapvei Oy, 73620 Kortteinen, Finland.

Diet

A complete pelleted rodent diet "Altromin 1324" from Chr. Petersen, DK- 4100 Ringsted, was available ad libitum.

Drinking water

The animals had free access to bottles with domestic quality drinking water. The drinking water was changed daily.

Animal randomisation and allocation

On the day of arrival the animals were randomly allocated to groups of 8 mice.

Body weight

The animals were weighed on the day of dosing.

Procedure

The test substances and reference compound were administered intraperitoneally in volumes of 20 ml per kg body weight 30 minutes before application of arachidonic acid to the ear.

All groups were treated with 20 µl arachidonic acid, 100 mg/ml in acetone, on the right ear.

The doses were as follows:

Drug	Dose, mg/kg
Vehicle, PBS	-, i.p.
Compound 92	1000 mg/kg, i.p.
Compound 92	300 mg/kg, i.p.
Compound 92	100 mg/kg, i.p.
Compound 33	1000 mg/kg, i.p.
Compound 33	300 mg/kg, i.p.
Compound 33	100 mg/kg, i.p.
Dexamethasone	6 mg/kg, i.p.
Dexamethasone	2 mg/kg, i.p.

One hour after the arachidonic acid application the mice were sacrificed, the ears cut from the tip with a punch biopsy knife (8 mm diameter) and weighed.

Mean weights and standard deviations were calculated. Relative ear oedema was assessed as the weight difference between right and left ear of each mouse expressed as percent of the left ear. Percent inhibition of the relative ear oedema compared with the vehicle treated groups was calculated for the test substance and reference compound treated groups.

Clinical signs

All visible signs of ill health and any behavioural changes were recorded daily during the study. Any deviation from normal was recorded with respect to time of onset, duration and intensity.

Statistics

Differences in relative ear oedema between the vehicle treated groups and the test substance and reference compound treated groups were tested for significance employing a non-parametric statistical method of analysis, the Mann-Whitney U test. The required level of significance was $p<0.05$.

All statistical analysis was performed employing the statistical software package Analyse-it v. 1.62.

RESULTS

Clinical signs

Arachidonic acid caused an inflammation in the right ears, which was visible after about 30 minutes. It could clearly be observed that the right ears were bright red and the left ears pale. The test articles to some extent prevented the reaction in the right ear. No test substance related adverse reactions were observed.

Ear oedema

The various concentrations of the test articles inhibited the relative oedema as shown in the table below:

Drug	Dose, mg per application	% Inhibition of relative ear oedema	Mann-Whitney U test
Vehicle, PBS	-, i.p.	-	-
Compound 92	1000 mg/kg, i.p.	65	p<0.0001
Compound 92	300 mg/kg, i.p.	44	p=0.0009
Compound 92	100 mg/kg, i.p.	14	p=0.0652
Compound 33	1000 mg/kg, i.p.	79	p=0.0002
Compound 33	300 mg/kg, i.p.	64	p<0.0001
Compound 33	100 mg/kg, i.p.	47	p=0.0052
Dexamethasone	6 mg/kg, i.p.	0	p=0.8359
Dexamethasone	2 mg/kg, i.p.	0	p=0.6008

Compound 92 and Compound 33 yielded a dose dependent and at all doses statistically significant inhibition of ear oedema. Dexamethasone, the reference compound, surprisingly did not inhibit ear oedema. This is attributed to a slower onset of action. Thus, the data imply that Compound 92 and Compound 33 have a faster onset of action than dexamethasone.

CONCLUSION

The data imply that systemically administered Compound 92 and Compound 33 are potent inhibitors of arachidonic acid induced ear oedema, with a faster onset of action than dexamethasone.

Example 178

Objective

The objective of this study is to assess the effect of a dose of a complex according to compared to the effect of the corresponding doses of the components of the complex. All compounds were systemically administered in the arachidonic acid induced ear inflammation test in the mouse, a commonly employed method for screening and

evaluation of antiinflammatory drugs. Methylprednisolone was employed as reference compound.

Test articles and vehicle

The test articles are the complex of the invention prepared according to example 92 (Compound 92 in the following) and its components salbutamol and glucosamine sulfate. The substances were obtained from Astion A/S, Denmark.

Animals

The study was performed in female BALB/ca mice from M & B A/S, DK-8680 Ry. At start of the acclimatisation period the mice were in the weight range of 20 g (+/- 5g).

Housing

The study took place in an animal room provided with filtered air. The temperature in the room was set at 21 - 23°C and the relative humidity to ≥30%. The room was illuminated to give a cycle of 12 hours light and 12 hours darkness. Light was on from 06.00 till 18.00 h.

The animals were housed in Macrolon type III cages (40x25x14 cm), 10 in each cage. The cages were cleaned and the bedding changed at least once a week.

Bedding

The bedding was sawdust (Tapvei 4HV) from Tapvei Oy, 73620 Kortteinen, Finland.

Diet

A complete pelleted rodent diet "Altromin 1324" from Chr. Petersen, DK- 4100 Ringsted, was available ad libitum.

Drinking water

The animals had free access to bottles with domestic quality drinking water. The drinking water was changed daily.

Animal randomisation and allocation

On the day of arrival the animals were randomly allocated to groups of 10 mice.

Body weight

The animals were weighed on the day of dosing and termination of the study.

Procedure

The test substances and reference compound were administered intraperitoneally in volumes of 20 ml per kg body weight 30 minutes before application of arachidonic acid to the ear.

All groups were treated with 20 µl arachidonic acid, 100 mg/ml in acetone, on the right ear.

The doses were as follows:

Drug	Dose, mg/kg
Vehicle, PBS	-, i.p.
Compound 92	1000 mg/kg, i.p.
Glucosamine sulfate	997 mg/kg, i.p.
Salbutamol	3.0 mg/kg, i.p.
Methylprednisolone	30 mg/kg, i.p.

One hour after the arachidonic acid application the mice were sacrificed, the ears cut from the tip with a punch biopsy knife (8 mm diameter) and weighed.

Mean weights and standard deviations were calculated. Relative ear oedema was assessed as the weight difference between right and left ear of each mouse expressed as percent of the left ear. Percent inhibition of the relative ear oedema compared with the vehicle treated groups was calculated for the test substance and reference compound treated groups.

Clinical signs

All visible signs of ill health and any behavioural changes were recorded daily during the study. Any deviation from normal was recorded with respect to time of onset, duration and intensity.

Statistics

Differences in relative ear oedema between the vehicle treated group and the other groups were tested for significance employing a non-parametric statistical method of analysis, the Mann-Whitney U test. The required level of significance will be $p<0.05$.
Similarly, the difference between the compound 92 treated group and the groups treated with the corresponding amounts of salbutamol and glucosamine sulfate respectively, were tested for significance to establish whether Compound 92 displays a significantly better effect than its components at the dose they occur in Compound 92. All statistical analysis was performed employing the statistical software package Analyse-it v. 1.62.

RESULTS

Clinical signs

Arachidonic acid caused an inflammation in the right ears, which was visible after about 30 minutes. It could clearly be observed that the right ears were bright red and the left ears pale. The test articles to some extent prevented the reaction in the right ear. No test substance related adverse reactions were observed.

Ear oedema

The various concentrations of the test articles inhibited the relative oedema as shown in the table below:

Drug	Dose, mg/kg	% Inhibition of relative ear oedema	Mann-Whitney U test
Vehicle, PBS	-	-	-
Compound 92	1000 mg/kg	73	p<0.0001
Glucosamine sulfate	997 mg/kg	9	p=0.1399
Salbutamol	3.0 mg/kg	55	p<0.0001
Methylprednisolone	30 mg/kg	55	p<0.0001

Compound 92 yielded a statistically significant inhibition of ear oedema. Glucosamine sulfate inhibited ear oedema mildly, and not statistically significantly, while Salbutamol inhibited ear oedema significantly. In the group receiving Compound 92 the relative ear oedema was 71% and 40% lower than in the groups receiving the corresponding doses of glucosamine sulfate and salbutamol, respectively. These differences were statistically significant, $p<0.0001$ and $p=0.0076$, respectively, and since Compound 92 reached a higher level of inhibition than the sum of inhibition of the corresponding doses of glucosamine sulfate and salbutamol, the data imply a synergistic effect.
Compound 92 yielded a 41% lower ear oedema than methylprednisolone and this difference was significant ($p=0.0021$).

CONCLUSION

The data imply that systemically administered Compound 92 is a potent inhibitor of arachidonic acid induced ear oedema and that the surprisingly strong inhibition is obtained through a synergistic effect between the components of the complex.

CLAIMS

1. A chemical complex comprising:

i) a beta-2 adrenoceptor agonist; and

ii) an aminosugar.

2. A chemical complex according to claim 1, wherein the Beta-2 adrenoceptor agonist is selected from the group consisting of bambuterol, bitolterol, carbuterol, clenbuterol, clorprenaline, dioxethedrine, dopexamine, ephedrine, epinephrine, etafedrine, ethylnorepinephrine, fenoterol, formoterol, hexoprenaline, isoetharine, isoproterenol, mabuterol, metaproterenol, methoxyphenamine, pirbuterol, procaterol, protokylol, reproterol, rimiterol, ritodrine, salbutamol (albuterol), salmeterol, soterenol, terbutaline, tretoquinol, tulobuterol, derivatives and salts thereof.

3. A chemical complex according to claim 1, wherein the aminosugar is selected from the group consisting of glucosamine, galactosamine, mannosamine, derivatives, polymers and salts thereof.

4. A chemical complex according to claim 3, wherein the aminosugar is N-acetylglucosamine, N-acetylgalactosamine or N-acetylmannosamine.

5. A chemical complex according to claim 3, wherein the aminosugar is a glucosamine sulfate.

6. A chemical complex according to any one of claims 1 to 5, wherein the Beta-2 adrenoceptor agonist and the aminosugar are present in a molar ratio of between about 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, such as about 1:100 to 100:1, such as about 1:10 to 10:1, also about 1:5 to 5:1, such as about 1:2 to 2:1.

7. A chemical complex according to any one of claims 1 to 5, wherein the Beta-2 adrenoceptor agonist and the optionally substitutes aminosugar are present in a mass ratio of between about 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, such as about 1:100 to 100:1, such as about 1:10 to 10:1, also about 1:5 to 5:1, such as about 1:2 to 2:1.

8. A composition comprising:
i) a beta-2 adrenoceptor agonist;
ii) an aminosugar; and optionally
iii) one or more acceptable excipients or carriers.

9. A composition according to claim 8, wherein the Beta-2 adrenoceptor agonist is selected from the group consisting of bambuterol, bitolterol, carbuterol, clenbuterol, clorprenaline,

dioxethedrine, dopexamine, ephedrine, epinephrine, etafedrine, ethylnorepinephrine, fenoterol, formoterol, hexoprenaline, isoetharine, isoproterenol, mabuterol, metaproterenol, methoxyphenamine, pirbuterol, procaterol, protokylol, reproterol, rimiterol, ritodrine, salbutamol (albuterol), salmeterol, soterenol, terbutaline, tretoquinol, tulobuterol, derivatives and salts thereof.

10. A composition according to any one of claims 9 to 9, wherein the aminosugar is selected from the group consisting of glucosamine, galactosamine, mannosamine derivatives, polymers, and salts thereof.

11. A composition according to claim 10, wherein the aminosugar is N-acetylglucosamine, N-acetylgalactosamine or N-acetylmannosamine.

12. A composition according to claim 10, wherein the aminosugar is a glucosamine sulfate.

13. A composition according to claim 8 comprising a
i) a complex as defined in any one of claims 1 to 7, and optionally
ii) one or more acceptable excipients or carriers.

14. A composition according to any one of claims 8 to 13 further comprising one or more therapeutically active agents.

15. A composition according to any one of claims 8 to 14 formulated as a pharmaceutical composition for oral, topical, transdermal, or parenteral administration.

16. A composition according to claim 15 formulated as a pharmaceutical composition for oral or topical administration.

17. A composition according to any one of claims 8 to 14 for use as a dietary supplement.

18. A use of a combination of a beta-2 adrenoceptor agonist and an aminosugar for the preparation of a medicament for the immunomodulation of a mammal, such as a human.

19. The use according to claim 18, wherein the medicament comprises a composition as defined by any one of claims 8 to 16 or a complex as defined in any one of claims 1 to 7.

20. The use according to claim 18, wherein the combination of the Beta-2 adrenoceptor agonist and an aminosugar is a chemical complex as defined in any one of claims 1 to 7.

21. The use according to claim 18, wherein the immunomodulation is selected from the group of suppression of hypersensitivity and suppression of inflammatory reactions.

22. The use according to claim 18, wherein the immodulation is associated with diseases and disorders selected from the group consisting of hypersensitivity skin disease, atopic eczema, contact dermatitis, seborrhoeic eczema, psoriasis, IgE mediated allergic reactions,

asthma, allergic rhinitis, anaphylaxis, autoimmune disease, chronic inflammatory disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout, osteoarthritis, pain and cancer.

23. The use according to any one of claims 18 to 22, wherein the Beta-2 adrenoceptor agonist and the aminosugar are together comprised in a single formulation or are each individually comprised in separate formulations.

24. The use to any one of claims 18 to 23, wherein the combination of a beta-2 adrenoceptor agonist and an aminosugar is administered by means of oral, topical, transdermal, or parenteral administration, or combinations thereof.

25. The use according any one of claims 18 to 24, wherein the medicament further comprises one or more therapeutically active agents.

26. The use according to claim 23, wherein the separate formulations are administered in a simultaneous or non-simultaneous manner.

27. The use according to claim 18, wherein the Beta-2 adrenoceptor agonist and the aminosugar are together comprised in a single formulation.

28. A method for immunomodulation in a mammal, such as a human, comprising the administration to said mammal of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof,
or a chemical complex comprising a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof.

29. The method according to claim 28 for the suppression of hypersensitivity and/or inflammatory reaction in a mammal, such as a human, comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, or a chemical complex comprising said combination or said salts to said mammal.

30. The method according to claim 28 for the treatment or prevention of hypersensitivity skin disease in a mammal, such as a human, comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, or a chemical complex comprising said combination or said salts to said mammal.

31. The method acording to claim 28 for the treatment or prevention of atopic eczema, contact dermatitis, seborrhoeic eczema and/or psoriasis in a mammal, such as a human, comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, or a chemical complex comprising said combination or said salts to said mammal.

32. The method according to claim 28 for the treatment or prevention of IgE mediated allergic reaction and/or condition in a mammal, such as a human, comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, or a chemical complex comprising said combination or said salts to said mammal.

33. The method according to claim 28 for the treatment or prevention of asthma, allergic rhinitis, and/or anaphylaxis in a mammal, such as a human, comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, or a chemical complex comprising said combination or said salts to said mammal.

34. The method according to claim 28 for the treatment or prevention of autoimmune disease and/or chronic inflammatory disease in a mammal, such as a human, comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, or a chemical complex comprising said combination or said salts to said mammal.

35. The method according to claim 28 for the treatment or prevention of diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout or osteoarthritis in a mammal, such as a human, comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, or a chemical complex comprising said combination or said salts to said mammal.

36. The method according to claim 28 for the alleviation of pain in a mammal, such as a human, comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, or a chemical complex comprising said combination or said salts to said mammal.

37. The method according to claim 28 for the treatment or prevention of cancer in a mammal, such as a human, comprising the administration of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, or a chemical complex comprising said combination or said salts to said mammal.

38. The method according to claim 28, wherein the combination of a beta-2 adrenoceptor agonist and an aminosugar is a chemical complex as defined in claims 1 to 7.

39. The method according to claims 28, wherein the combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, are together comprised in a single formulation or are each individually comprised in separate formulations.

40. The method according to claim 28, wherein the combination of a beta-2 adrenoceptor agonist and an aminosugar is administered by means of oral, topical, transdermal, or parenteral administration, or combinations thereof.

41. The method according to claim 39, wherein the separate formulations are administered in a simultaneous or non-simultaneous manner.

42. The method according to claim 41, wherein the separate formulations further comprises one or more therapeutically active substances.

43. The method according to any one of claim 39, wherein the combination of a beta-2 adrenoceptor agonist and an aminosugar are together comprised in a single formulation.

44. The method according to claim 43, wherein the single formulation further comprises one or more therapeutically active substances.

45. A process for the preparation of a complex comprising i) a beta-2 adrenoceptor agonist; and ii) an aminosugar, comprising the steps of:
i) dissolving said beta-2 adrenoceptor and said aminosugar in a volatile solvent or a mixture of volatile solvents; and
ii) removing said suitable solvent so as to obtain a moisture content of at the most 5% w/w.

46. The process according to claim 45, wherein the volatile solvent is selected from the group consisting of water, water-miscible volatile organic solvents and mixtures thereof.

47. The process according to any one of claims 45 to 46, wherein the solvent is removed by spray drying or freeze-drying.

48. The process according to to any one of claims 45 to 47, wherein the moisture content is at the most 3% w/w, preferably at the most about 2% w/w, more preferably at the most about 1% w/w, even more preferably at the most about 0.5 % w/w, most preferably at the most about 0.2 % w/w.